ORIGINAL ARTICLE

Trial of Spesolimab for Generalized Pustular Psoriasis

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ABSTRACT

BACKGROUND

Generalized pustular psoriasis (GPP) is a rare, life-threatening, inflammatory skin disease characterized by widespread eruption of sterile pustules. Interleukin-36 signaling is involved in the pathogenesis of this disorder. Spesolimab, a humanized anti–interleukin-36 receptor monoclonal antibody, is being studied for the treatment of GPP flares.

METHODS

In a phase 2 trial, we randomly assigned patients with a GPP flare in a 2:1 ratio to receive a single 900-mg intravenous dose of spesolimab or placebo. Patients in both groups could receive an open-label dose of spesolimab on day 8, an open-label dose of spesolimab as a rescue medication after day 8, or both and were followed to week 12. The primary end point was a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of 0 (range, 0 [no visible pustules] to 4 [severe pustulation]) at the end of week 1. The key secondary end point was a GPPGA total score of 0 or 1 (clear or almost clear skin) at the end of week 1; scores range from 0 to 4, with higher scores indicating greater disease severity.

RESULTS

A total of 53 patients were enrolled: 35 were assigned to receive spesolimab and 18 to receive placebo. At baseline, 46% of the patients in the spesolimab group and 39% of those in the placebo group had a GPPGA pustulation subscore of 3, and 37% and 33%, respectively, had a pustulation subscore of 4. At the end of week 1, a total of 19 of 35 patients (54%) in the spesolimab group had a pustulation subscore of 0, as compared with 1 of 18 patients (6%) in the placebo group (difference, 49 percentage points; 95% confidence interval [CI], 21 to 67; P<0.001). A total of 15 of 35 patients (43%) had a GPPGA total score of 0 or 1, as compared with 2 of 18 patients (11%) in the placebo group (difference, 32 percentage points; 95% CI, 2 to 53; P=0.02). Drug reactions were reported in 2 patients who received spesolimab, in 1 of them concurrently with a drug-induced hepatic injury. Among patients assigned to the spesolimab group, infections occurred in 6 of 35 (17%) through the first week; among patients who received spesolimab at any time in the trial, infections had occurred in 24 of 51 (47%) at week 12. Antidrug antibodies were detected in 23 of 50 patients (46%) who received at least one dose of spesolimab.

CONCLUSIONS

In a phase 2 randomized trial involving patients with GPP, the interleukin-36 receptor inhibitor spesolimab resulted in a higher incidence of lesion clearance at 1 week than placebo but was associated with infections and systemic drug reactions. Longer and larger trials are warranted to determine the effect and risks of spesolimab in patients with pustular psoriasis. (Funded by Boehringer Ingelheim; Effisayil 1 ClinicalTrials.gov number, NCT03782792.)

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*A complete list of the members of the Effisayil 1 Trial Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

Generalized pustular psoriasis (GPP) is a rare, potentially life-threatening autoinflammatory skin disease characterized by widespread eruption of sterile, visible pustules that occurs with or without systemic symptoms of pain, fever, general malaise, fatigue, and extracutaneous manifestations such as arthritis and neutrophilic cholangitis.[1-4] The clinical course of GPP can be relapsing with recurrent flares or persistent with intermittent flares.[1,2] Mortality ranges from 2 to 16%, and deaths have been attributed to septic shock and cardiorespiratory failure.[3,5-8] The frequency of flares varies among patients, and flares may be spontaneous or triggered by upper respiratory tract infections, stress, medication, medication withdrawal, and pregnancy.[3,6,9-14] The disease has adverse effects on quality of life.[15,16]

Biologic agents that inhibit tumor necrosis factor α (adalimumab, infliximab, and certolizumab pegol), interleukin-17 or interleukin-17 receptor (secukinumab, brodalumab, and ixekizumab), and interleukin-23 (risankizumab and guselkumab) are approved for the treatment of GPP in Japan, Taiwan, and Thailand on the basis of small trials of these drugs involving patients with plaque psoriasis and small, nonrandomized trials involving patients with GPP.[8,17-21] There are no approved therapies for the disease in the United States or Europe, and management has included cyclosporine, retinoids, methotrexate, and biologic agents.[8,17]

The role of the interleukin-36 pathway in GPP is supported by the finding of loss-of-function mutations in the interleukin-36 receptor antagonist gene (*IL36RN*) and associated genes (*CARD14*, *AP1S3*, *SERPINA3*, and *MPO*) and by the overexpression of interleukin-36 cytokines in GPP skin lesions.[10,22-25] Clinical improvements with spesolimab, a humanized anti–interleukin-36 receptor monoclonal antibody, were observed in an open-label phase 1 study involving seven patients presenting with a GPP flare.[26]

We conducted a phase 2 randomized trial (Effisayil 1) to investigate the efficacy and safety of spesolimab as compared with placebo in patients presenting with a GPP flare. Because acute and severe flares of this disorder are life-threatening, a single dose of the drug with a placebo-controlled period of 1 week was chosen for the randomized phase of the trial design, and patients in both groups were offered the opportunity to receive open-label spesolimab on day 8. At week 12, the end of the trial, patients were offered enrollment into a 5-year open-label extension trial of spesolimab (ClinicalTrials.gov number, NCT03886246).

Methods

Trial Design

This phase 2, multicenter, randomized, double-blind, placebo-controlled trial was conducted between February 20, 2019, and January 5, 2021, and patients were enrolled at 37 sites in 12 countries. Because GPP is a rare disorder, and because estimates of prevalence at the time of planning the trial suggested that GPP was approximately five times more common in Asia than in Europe and the United States,[7,27] the trial sites were chosen accordingly. (The trial investigators and their locations are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org.) Although data from published literature are lacking, our clinical experience has been that the disease occurs even less frequently among Black persons than among White persons.

Patients who presented with a GPP flare were randomly assigned in a 2:1 ratio to receive a single intravenous dose of 900 mg of spesolimab or placebo (Fig. 1). (The preparation of placebo is described in Table 4.1.1:2 in the protocol, available at NEJM.org.) Randomization was performed with the use of an interactive response system, with the stratification factor of Japanese as compared with non-Japanese ethnic group.

Patients and investigators were unaware of whether spesolimab or placebo was administered on day 1 throughout the trial until the database was locked for analyses. On day 8, patients from both groups were eligible to receive a single, open-label, intravenous dose of 900 mg of spesolimab (which led to a crossover from placebo to open-label spesolimab for some patients) if they had persistent symptoms, on the basis of a predefined threshold that consisted of a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) total score of 2 or higher at the end of week 1 (range, 0 [clear skin] to 4 [severe disease]) and a clinician assessment of GPP severity based on a modified Physician Global Assessment and a GPPGA pustulation subscore of 2 or higher at week 1 (range, 0 [no

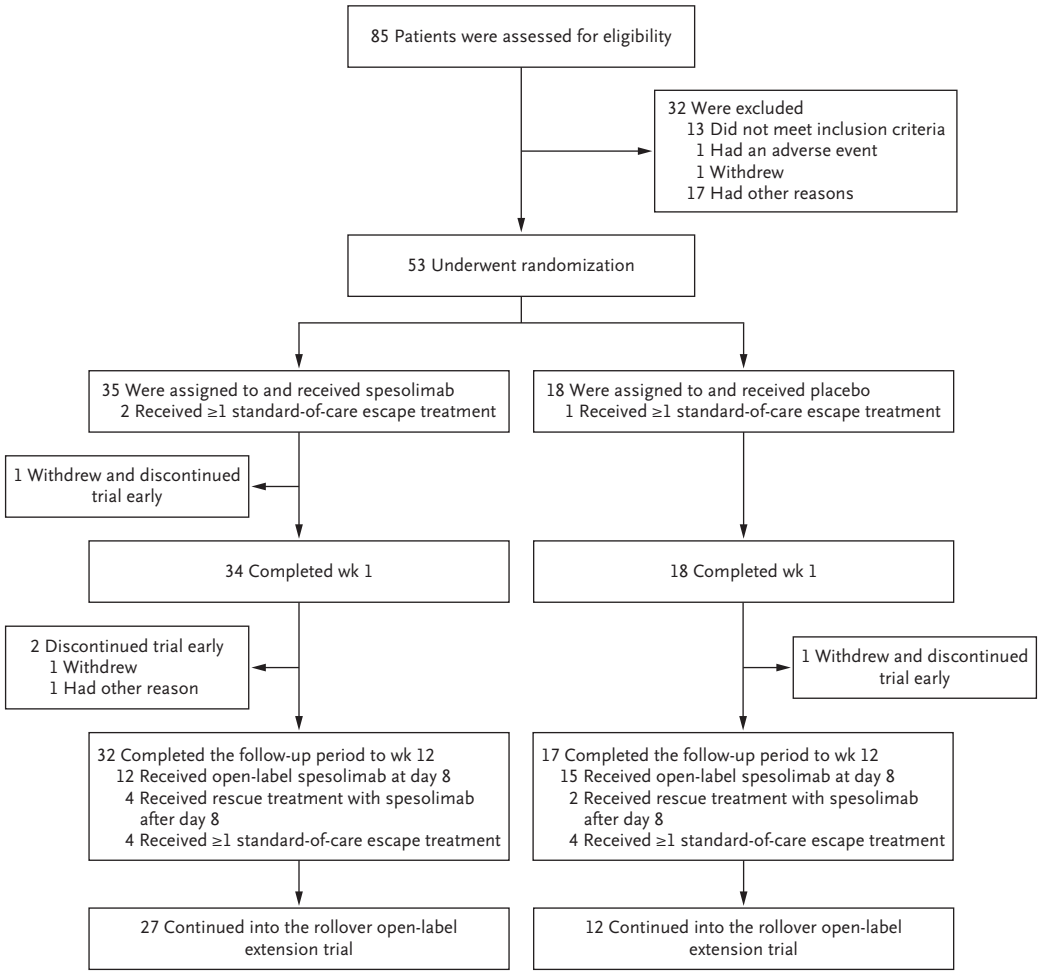

Figure 1. Randomization and Follow-up.

Among patients who were excluded before randomization, other reasons for exclusion included completion of the current trial, achievement of the global recruitment target, and the absence of a flare within the 6-month screening period. Escape treatment was defined as standard-of-care therapy, according to the treating physician's choice, that was allowed for patients who had worsening of disease that warranted immediate treatment during week 1 and for patients with disease worsening who did not qualify for a rescue medication with open-label spesolimab after week 1. Throughout the follow-up period to week 12, patients were unaware of whether spesolimab or placebo was administered on day 1, but patients could be eligible for an open-label dose of spesolimab at day 8. Patients who did not continue into the open-label extension trial were to be followed for 16 weeks after the placebo dose or the last dose of spesolimab (i.e., on day 1, on day 8 if open-label spesolimab was given, or whenever rescue treatment with open-label spesolimab was administered after day 8).

visible pustules] to 4 [severe pustulation]). The GPPGA total score is the average of the subscores for pustulation, erythema, and scaling (see the Supplementary Appendix).

After week 1, rescue treatment with a single intravenous dose of 900 mg of spesolimab could be administered in case of reoccurrence of a flare (defined as an increase of ≥2 points in both the GPPGA total score and the pustulation subscore after a GPPGA total score of 0 or 1 had been reached). Patients who had clinical improvement and completed the trial without flare symptoms were eligible to enter a 5-year open-label extension trial (noted above). Escape treatment was defined as standard-of-care therapy, according to the treating physician's choice, that

was allowed for patients who had worsening of disease that warranted immediate treatment during week 1 and for patients with disease worsening who did not qualify for a rescue medication with open-label spesolimab after week 1. The use of escape treatment in the first week was essential for patient safety because flares of GPP are potentially life-threatening. Any patient who received escape medication was considered not to have had a response (nonresponse) in the analysis for the primary and key secondary evaluation at week 1. Further details of the trial design are provided in the protocol and in Figure S1 in the Supplementary Appendix and have been published previously.[28]

TRIAL OVERSIGHT AND ROLE OF THE SPONSOR

The sponsor, Boehringer Ingelheim, designed the trial, analyzed the data, provided spesolimab and placebo, and paid for professional writing assistance. The academic authors were not restricted by the sponsor from publishing the results of the trial. Confidentiality agreements were in place between the authors and Boehringer Ingelheim. The trial was conducted in accordance with the trial protocol, the International Council for Harmonisation Good Clinical Practice guidelines, Regulation (EU [European Union]) No. 536/2014, the Japanese Good Clinical Practice regulations, and applicable local regulations. The trial was approved by ethics committees of participating institutions and countries. All the patients provided written informed consent.

PATIENTS

Patients who were 18 to 75 years of age were eligible for enrollment if they had a history of GPP consistent with the diagnostic criteria of the European Rare and Severe Psoriasis Expert Network.[1] Analyses of coding sequences for the three main GPP-associated genes (*IL36RN*, *CARD14*, and *AP1S3*) were performed on DNA extracts from blood samples, but patients were enrolled without regard to *IL36RN* mutation status. Patients had to have a GPP flare of moderate-to-severe intensity (defined as a GPPGA total score of ≥3, new or worsening pustules, a GPPGA pustulation subscore of ≥2, and ≥5% of body-surface area with erythema and the presence of pustules). Key exclusion criteria were plaque psoriasis without pustules or with pustules restricted to psoriatic plaques, drug-triggered acute generalized exanthematous pustulosis, an immediate life-threatening flare of GPP warranting intensive care treatment, and current treatment with methotrexate, cyclosporine, retinoids, or other restricted medications, as listed in Table S2.

END POINTS

The primary end point was a GPPGA pustulation subscore of 0 (no visible pustules) at the end of week 1. The key secondary end point was a GPPGA total score of 0 or 1 (clear or almost clear skin) at the end of week 1. Secondary end points were mostly assessed at week 4 (some patients received open-label spesolimab at the end of week 1). Secondary end points at week 4 (after the randomized phase of the trial) included a 75% or greater decrease in the score on the Psoriasis Area and Severity Index (PASI) for Generalized Pustular Psoriasis (GPPASI 75) (the GPPASI score is an adaptation of the PASI score in which the induration component is replaced by a pustule component; scores range from 0 [least severe] to 72 [most severe]) (see the Supplementary Appendix); the change from baseline in the assessment of pain on a visual analogue scale (pain VAS; scores range from 0 [no pain] to 100 [severe pain]); the change from baseline in the score on the Psoriasis Symptom Scale (PSS, which involves patient-reported psoriasis pain, redness, itching, and burning; scores range from 0 to 16, with higher scores indicating more severe symptoms); and the change from baseline in the score on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue, which involves the patient-reported effect of fatigue on daily activities; scores range from 0 to 52, with lower scores indicating a greater effect). Additional secondary end points were assessed at week 1, week 4, or both, as listed in the Supplementary Appendix, the protocol, and the statistical analysis plan (available with the protocol at NEJM.org). Details of prespecified trial end points, changes in prespecified end points by amendment to the protocol and statistical analysis plan, and exploratory end points are listed in Table S3.

Safety events at week 1 (through the first 8 days of the trial) and through week 12 included adverse events that began or worsened between the start of spesolimab or placebo administration and the end of the residual-effect

period (16 weeks after the placebo dose or the last dose of spesolimab). Adverse events were assessed by the trial investigators, who were unaware of the trial-group assignments. During the course of the trial, occurrences of adverse events were collected, documented on the electronic case reports, and reported to the sponsor by the investigators. The intensity of the adverse events was assessed by the investigators and graded according to Rheumatology Common Toxicity Criteria, version 2.0, developed by the Outcome Measures in Rheumatology (OMERACT) organization.[29]

STATISTICAL ANALYSIS

We estimated that a sample of 51 patients would provide 90% or greater power to detect any difference between spesolimab and placebo with an assumed response of 0.6 and 0.1, respectively, for both the primary and key secondary end points and a type I error rate of less than 0.025 (one-sided), which can be considered to be a type I error rate of less than 0.05 with a two-sided test. The primary end point and key secondary end point were analyzed in the randomized intention-to-treat population with an exact Suissa–Shuster z-pooled test. This is a one-sided test; the two-sided P value was reported by doubling the one-sided P value of 0.1.[30] Confidence intervals around the risk difference were calculated with the use of the Chan and Zhang method for the primary end point and all binary secondary end points.[31] To control familywise type I error, the primary end point and key secondary end point (both assessed at day 8 [end of week 1]) were tested in a hierarchical manner at a two-sided P value of less than 0.05.[32] If the between-group difference in the primary end point was not significant, the key secondary end points would not be tested.

The protocol and statistical analysis plan called for hierarchical testing of four subsequent secondary end points (GPPASI 75 and change from baseline in scores on the pain VAS, PSS, and FACIT-Fatigue), all at week 4; however, randomization to trial groups no longer pertained after week 1 because 15 of the 18 patients who were assigned to receive placebo received open-label spesolimab on day 8 and were imputed with nonresponse or the worst possible outcome. Therefore, comparisons according to randomized treatment as originally planned were noninformative; the changes at week 4 for these end points are reported descriptively for the following groups: all patients randomly assigned to receive spesolimab (patients who received one dose [day 1 only] or two doses [day 1 plus day 8]), patients randomly assigned to receive spesolimab who did not receive open-label spesolimab on day 8 (patients who received spesolimab on day 1 only), patients randomly assigned to receive spesolimab who received open-label spesolimab on day 8 (patients who received spesolimab on day 1 plus day 8), and patients randomly assigned to receive placebo who received open-label spesolimab on day 8 (patients who received one dose of spesolimab on day 8). For binary end points, patients with missing data were considered not to have had the respective end-point event. For continuous end points, the last-observation-carried-forward method was used for imputation. No interim analyses were performed. We performed post hoc sensitivity analyses of the primary and key secondary end points using linear regression with adjustment for the imbalanced covariates at baseline, including sex, race, and GPPASI score; no conclusions can be drawn from these analyses.

RESULTS

PATIENTS

Of 85 patients screened, 53 were enrolled: 35 were assigned to receive 900 mg of spesolimab and 18 to receive placebo (Fig. 1, Table 1, and Table S1). The demographic and clinical characteristics of the patients at baseline differed between the trial groups with respect to female sex (60% in the spesolimab group and 83% in the placebo group) and Asian race (46% and 72%, respectively). Furthermore, the median GPPASI total score at baseline was 27.4 in the spesolimab group and 20.9 in the placebo group (Table 1). At the time of randomization, 19% of all the patients had a GPPGA total score of 4 (severe), and most patients had a GPPGA pustulation subscore of 3 or 4 (high or very high density of pustules) and impaired quality of life and clinical burden, as indicated by scores on the Dermatology Life Quality Index (DLQI), pain VAS, PSS, and FACIT-Fatigue. Seven patients, 5 in the spesolimab group and 2 in the placebo group, had *IL36RN* mutations (Table 1). Most patients did not have *CARD14* mutations (38 patients without) or *AP1S3* mutations (42 without) (Table S4).

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Spesolimab (N=35)	Placebo (N=18)
Age — yr	43.2±12.1	42.6±8.4
Weight — kg	73.7±24.0	68.8±26.6
Female sex — no. (%)	21 (60)	15 (83)
Race — no. (%)†		
Asian	16 (46)	13 (72)
White	19 (54)	5 (28)
GPPGA total score — no. (%)‡		
3	28 (80)	15 (83)
4	7 (20)	3 (17)
GPPGA pustulation subscore — no. (%)§		
2	6 (17)	5 (28)
3	16 (46)	7 (39)
4	13 (37)	6 (33)
Median GPPASI total score (IQR)¶	27.4 (15.5–36.8)	20.9 (12.0–32.0)
IL36RN mutation — no. (%)‖		
Yes	5 (14)	2 (11)
No	24 (69)	12 (67)

* Plus–minus values are means ±SD. IQR denotes interquartile range.
† Race was reported by the patient.
‡ Scores on the Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) range from 0 (clear skin) to 4 (severe disease).
§ GPPGA pustulation subscores range from 0 (no visible pustules) to 4 (severe pustulation).
¶ Scores on the Psoriasis Area and Severity Index for Generalized Pustular Psoriasis (GPPASI) range from 0 (least severe) to 72 (most severe).
‖ Five patients had homozygous mutations (four with p.Leu27Pro and one with p.Ser113Leu), and two patients had heterozygous mutations (p.Ser113Leu; p.Ser113Leu/p.Val44Met). At the date of database lock (January 18, 2021), DNA sequencing (targeted resequencing with Illumina MiSeq) was not yet completed in three patients, and samples from seven patients were missing.

A total of 52 of the 53 enrolled patients completed the first week of the trial. Data for 1 patient in the spesolimab group were missing for the primary and key secondary end points and were imputed as no response. At day 8, a total of 12 patients (34%) in the spesolimab group and 15 patients (83%) in the placebo group received an open-label dose of spesolimab. After day 8, a total of 32 patients (91%) who were randomly assigned to receive spesolimab and 17 patients (94%) who were randomly assigned to receive placebo completed the 12-week follow-up period, during which 4 and 2 patients, respectively, received rescue treatment with spesolimab. After completing 12 weeks of treatment, 39 patients were enrolled in the open-label extension trial (Fig. 1).

EFFICACY

Primary and Key Secondary Efficacy End Points

At the end of week 1, a total of 19 of the 35 patients (54%) who were assigned to the spesolimab group and 1 of the 18 patients (6%) who were assigned to the placebo group had a GPPGA pustulation subscore of 0 (no visible pustules) (difference, 49 percentage points; 95% confidence interval [CI], 21 to 67; P<0.001) (Table 2). A total of 15 patients (43%) who were assigned to the spesolimab group and 2 patients (11%) who were assigned to the placebo group had a GPPGA total score of 0 or 1 (clear or almost clear skin) (difference, 32 percentage points; 95% CI, 2 to 53; P=0.02) (Table 2). The GPPGA pustulation subscores and the GPPGA total scores over time according to trial-group assign-

Table 2. Primary and Key Secondary Efficacy End Points.

End Point	Spesolimab (N=35)	Placebo (N=18)
Primary end point: GPPGA pustulation subscore of 0 at wk 1		
Response — no. of patients (%)	19 (54)	1 (6)
Difference vs. placebo (95% CI) — percentage points	49 (21–67)	
P value*	<0.001	
Key secondary end point: GPPGA total score of 0 or 1 at wk 1		
Response — no. of patients (%)	15 (43)	2 (11)
Difference vs. placebo (95% CI) — percentage points	32 (2–53)	
P value*	0.02	

* Shown are two-sided P values calculated by means of the Suissa–Shuster z-pooled test.

ment are shown in Figures S2 and S3. The results of the post hoc sensitivity analyses of the primary and key secondary end points to adjust for the observed baseline imbalances in sex, race, and GPPASI score were consistent with the results of the primary analysis (Tables S5 and S6).

Exploratory Efficacy End Points after Day 8

After week 1, a total of 15 of 18 patients who were assigned to the placebo group received open-label spesolimab on day 8; thus, planned hierarchical testing of secondary end points at week 4 was noninformative. Instead, the secondary end points were reported descriptively in four groups that reflected the treatment paths after day 8: all 35 patients randomly assigned to receive spesolimab (patients who received one dose [day 1 only] or two doses [day 1 plus day 8]), 23 patients randomly assigned to receive spesolimab who did not receive open-label spesolimab on day 8 (day 1 only), 12 patients randomly assigned to receive spesolimab who received open-label spesolimab on day 8 (day 1 plus day 8), and 15 patients randomly assigned to receive placebo who received open-label spesolimab on day 8. Descriptive analyses of the GPPGA pustulation subscore and the GPPGA total score in these subgroups over time are reported in Figures S4 and S5, and the secondary end points of GPPASI 75 and change from baseline in scores on the pain VAS, PSS, and FACIT-Fatigue at week 4 are reported in Table S7. For the 35 patients assigned to the spesolimab group who received one dose (day 1 only) or two doses (day 1 plus day 8), descriptive results for GPPASI score, GPPASI 75, pain VAS score, DLQI score, neutrophil counts, and C-reactive protein levels over a period of 12 weeks are reported in Figure S6. The descriptive results for the 3 remaining patients who were assigned to the placebo group and did not receive spesolimab on day 8 are not reported.

SAFETY

Through the first week of treatment, adverse events were reported in 66% of the patients assigned to the spesolimab group and 56% of those assigned to the placebo group. Pyrexia occurred in 6% of the patients who received spesolimab and in 22% of those who received placebo; all pyrexia events occurred in the context of the underlying GPP flare, but pyrexia attributable to the drug cannot be ruled out (Table 3). Infections were reported in 17% of the patients in the spesolimab group and in 6% of those in the placebo group through the first week (Table S8). At week 1, in the spesolimab group, there were two cases of urinary tract infection and one case each of various other infections. Serious adverse events were reported in 6% of the patients who received spesolimab and in none of the patients who received placebo in the first week.

At week 12, a total of 82% of the patients who received at least one dose of spesolimab (including those assigned to the placebo group who received open-label spesolimab at day 8) had an adverse event, and 12% had a serious adverse event; in the spesolimab group, the percentages of patients with adverse events remained unchanged or increased and the time-adjusted incidence rates decreased from week 1 to week 12 (Table 3). Infections were reported in 47% of the patients. There were three cases each of urinary tract infection and influenza; two cases each of folliculitis, otitis externa, upper respiratory tract infection, and pustule; and one case each of other infections. Symptoms that were observed in two patients who received spesolimab were reported as a drug reaction with eosinophilia and systemic symptoms (DRESS) with RegiSCAR (European Registry of Severe Cutaneous Adverse Reactions) scores of 1 and 3 (a score of <2 indicates no DRESS, a score of 2 or 3 possible DRESS, a score of 4 or 5 probable DRESS, and a score of >5 definite DRESS).[33] Details of these two cases are provided in the Supplementary Appendix. Antidrug antibodies were detected at a median of 2.3 weeks after spesolimab administration. Antidrug antibodies were detected in 23 of 50 patients (46%) who received at least one dose of spesolimab.

DISCUSSION

This randomized trial of a single intravenous dose of the humanized anti–interleukin-36 receptor monoclonal antibody spesolimab in patients with a flare of GPP showed that at 1 week there was better clearance of lesions with spesolimab than with placebo. Infections were more frequent with spesolimab, although there was

Table 3. Summary of Adverse Events.*

Event	Week 1				Week 12†	
	Spesolimab (N=35)		Placebo (N=18)		Spesolimab (N=51)	
	No. (%)	Rate per 100 patient-yr	No. (%)	Rate per 100 patient-yr	No. (%)	Rate per 100 patient-yr
Any adverse event	23 (66)	5874.7	10 (56)	4623.4	42 (82)	981.5
Severe adverse event: RCTC grade 3 or 4	2 (6)	309.5	1 (6)	304.4	5 (10)	40.9
Investigator-defined drug-related adverse event	10 (29)	1747.6	5 (28)	1773.1	28 (55)	353.5
Serious adverse event	2 (6)	309.5	0	—	6 (12)	49.7
Death	0	—	0	—	0	—
Adverse event leading to discontinuation of spesolimab or placebo	0	—	0	—	0	—
Common adverse events‡						
Pyrexia	2 (6)	313.5	4 (22)	1404.8	5 (10)	41.3
Dizziness	0	—	2 (11)	619.1	0	—
Serious adverse events						
Drug reaction with eosinophilia and systemic symptoms	1 (3)	154.1	0	—	2 (4)	15.9
Urinary tract infection	1 (3)	154.1	0	—	1 (2)	7.8
Drug-induced hepatic injury§	1 (3)	154.1	0	—	1 (2)	7.8
Arthritis	1 (3)	152.2	0	—	1 (2)	7.8
Worsening of chronic plaque psoriasis¶	0	—	0	—	1 (2)	7.8
Influenza	0	—	0	—	1 (2)	7.7
Squamous-cell carcinoma of skin	0	—	0	—	1 (2)	7.7

* Shown are adverse events that occurred between the start of spesolimab or placebo administration and the end of the residual-effect period (16 weeks after the placebo dose or the last dose of spesolimab). Adverse events were coded with the use of the *Medical Dictionary for Drug Regulatory Activities*, version 23.1. The severity of adverse events was graded according to the Rheumatology Common Toxicity Criteria (RCTC), version 2.0. Pustular psoriasis was excluded as an adverse event from this safety analysis.

† The data set at week 12 includes patients assigned to the spesolimab group who received up to three doses of spesolimab and patients assigned to the placebo group who received open-label spesolimab at or after day 8. All adverse events from the first use of spesolimab to the residual-effect period of the last spesolimab dose are included.

‡ Shown are adverse events that occurred in at least 10% of the patients in any trial group.

§ Drug-induced hepatic injury was reflected by an increase in aminotransferase levels and was considered to be a systemic symptom of drug reaction with eosinophilia and systemic symptoms.

¶ Events involving the worsening of chronic plaque psoriasis are reflective of nonpustular psoriasis; these events were not captured in the efficacy end points.

no particular pathogen or affected organ. Two patients who received spesolimab had DRESS with RegiSCAR scores of 1 and 3.

At the end of the 1-week randomized period, approximately one third of the patients in the spesolimab group and most patients in the placebo group received open-label spesolimab and were followed for 12 weeks. Because 15 of the 18 patients who were assigned to the placebo group received open-label spesolimab, the effect of spesolimab as compared with that of placebo could not be determined after week 1. The episodic nature and variable severity of GPP flares present challenges in designing trials for patients with this disease. It may not be safe or reasonable, for example, to continue placebo administration for more than a week or similarly brief period once a flare has occurred. Furthermore, the clinical course of this disorder varies between and within patients and can be relapsing with recurrent flares or persistent with intermittent flares.

In addition to the brief randomized period of treatment, this trial has other limitations, in-

cluding the small number of enrolled patients. However, the effect sizes for the primary and key secondary end points at week 1 were large. The option for patients to receive open-label treatment with spesolimab at the end of the 1-week randomized period, if a prespecified threshold for severity was met, meant that most patients in the placebo group received spesolimab, and comparative analyses after week 1 reflected either continuous or delayed (by 1 week) treatment with spesolimab and were not subject to conventional analyses comparing two trial groups. There were also baseline imbalances between the trial groups with respect to sex, race, and GPPASI score; however, the results of post hoc sensitivity analyses of the primary and key secondary end points that were adjusted for the imbalances were consistent with the results of the primary analysis.

The results of the current trial with a single infusion of spesolimab add to findings from a previous open-label study of spesolimab[26] and support the hypothesis that interleukin-36 is involved in the pathogenesis of GPP. Long-term administration of spesolimab is being evaluated with a subcutaneous formulation in the 5-year open-label extension trial noted above and the Effisayil 2 trial on prevention of flares (ClinicalTrials.gov number, NCT04399837).

In this phase 2 trial involving patients with flares of GPP, intravenous spesolimab resulted in higher rates of clearance of pustular lesions at 1 week than placebo but was associated with infections and systemic reactions. Longer and larger trials are warranted to determine the effect and safety of spesolimab in patients with pustular psoriasis.

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APPENDIX

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